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EXAMINER

GIBBS, TERRA C

ART UNIT PAPER NUMBER

1635

DATE MAILED: 09/08/2003

13

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/945,131

Applicant(s)

SIROIS ET AL.

Examiner

Terra C. Gibbs

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 10 June 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1 and 3-20 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1 and 3-20 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other:

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DETAILED ACTION

This Office Action is a response to the Amendment filed April 28, 2003, in Paper No. 11.

Claim 2 has been canceled. Claims 1, 17, and 18 have been amended.

Claims 1 and 3-20 are pending in the instant application.

Response to Amendment

Applicants Declaration under 37 CFR 1.132, filed April 28, 2003 in Paper No. 11 is acknowledged.

Applicants Amendment to include a specific reference to the prior application(s) in the first sentence of the specification is acknowledged.

Applicants Declarations, filed April 28, 2003 and June 10, 2003, to correct non-initialed and/or non-dated alterations are acknowledged.

Claim Objections

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 17 was objected to because of the following informalities: This rejection is withdrawn in view of Applicants Amendment to claim 17 correct a typographical error.

Claim Rejections - 35 USC § 112

Claim 18 was rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. This rejection is withdrawn in view of Applicants Amendment to claim 18 to correct insufficient antecedent basis, filed April 28, 2003, in Paper No. 11.

Claim Rejections - 35 USC § 102

Claims 1-4, 6-8, 10-13 and 20 were rejected under 35 U.S.C. 102(b) as being anticipated by Sirois et al. (Circulation, 1997 Vol. 95:669-676). This rejection is withdrawn in view of Applicants Amendment to the claims, filed April 28, 2003, in Paper No. 11 and Applicants Declaration, filed June 10, 2003 in Paper No. 12.

Claims 1-20 were rejected under 35 U.S.C. 102(b) as being anticipated by Rosenberg et al. [WO 93/08845]. This rejection is withdrawn in view of Applicants Amendment to the claims, filed April 28, 2003, in Paper No. 11.

Claim Rejections - 35 USC § 103

Claims 1-20 were rejected under 35 U.S.C. 103(a) as being unpatentable over Sirois et al. (Circulation, 1997 Vol. 95:669-676) and Rosenberg et al. [WO 93/08845] in further view of Rosenberg et al. [U.S. Patent No. 5,593,974]. This rejection is withdrawn in view of Applicants Amendment to the claims, filed April 28, 2003, in Paper No. 11.

Priority

The reference to priority in the first line of the Specification should be updated where patent applications have been abandoned. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 6, 8, 9, 11, and 16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 6 recites the limitation "said oligonucleotide sequence" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1, from which claim 6 depends, has the term "oligonucleotide", not "oligonucleotide sequence". Correction is required.

Claims 8 and 9 recite the limitation "wherein the treatment" in line 1. There is insufficient antecedent basis for this limitation in the claims because claim 7, from which claims 8 and 9 depend, has the term "wherein said at least one oligonucleotide is treated", not "treatment". Correction is required.

Claim 11 recites the limitation "target nucleic acid sequence" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 1, from which claim 11 depends, has the term "oligonucleotide", not "target nucleic acid sequence". Correction is required.

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Claim 16 recites the limitation "hydrogel material" in line 1. There is insufficient antecedent basis for this limitation in the claim because claim 15, from which claim 16 depends, has the term "hydrogel comprises a material", not "hydrogel material". Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 3-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant claims read on a method for preventing restenosis by improving reendothelialization, vascular endothelial function and by reducing smooth muscle migration and/or proliferation comprising the administration of at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit.

The claimed invention encompasses nucleic acid compounds encoding all forms of the PDGFR- β subunit gene, which includes sequences from any species, mutated sequences, polymorphic and allelic variants, splice variants, sequences that have an unspecified degree of identity (similarity, homology), and so forth. The specification as filed provides only a description of two oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit (see SEQ ID NOs. 1 and 2).

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The specification as filed provides only a description of two oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit (see SEQ ID NOs. 1 and 2). However, the specification as filed, does not provide sufficient description that would allow one of skill in the art to use SEQ ID NOs. 1 and 2 to predict the structures of oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit isolated from other sources, including all polymorphic, allelic and splice variants of this mRNA.

The specification fails to describe the complete structure of a representative number of species of the claimed genus. See the Guidelines for Examination of Patent Applications Under the 35 USC 112 ¶ 1, "Written Description" Requirement (Vol. 66, No. 4, pages 1099-1111). These guidelines state that: "To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art can reasonably conclude that the inventor had possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing that the invention was "ready for patenting" such as by the disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that applicant was in possession of the claimed invention." In the instant case, the specification does not describe or identify characteristics that can be used to distinguish species of the claimed genus.

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Additionally, “[T]he skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides and/or proteins, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. The nucleic acid itself is required. See Fiers v. Revel, 25 USPQ2d 1601, 1606 (CAFC 1993) and Amgen Inc. V. Chugai Pharmaceutical Co. Ltd., 18 USPQ2d 1016. In Fiddes v. Baird, 30 USPQ2d 1481, 1483, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class. The specification provided only the bovine sequence.”

Applicant's specification does not provide a sufficient number of representative species of oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit, which would allow one of skill in the art to predict the structures of all members of the claimed genus of compounds. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Therefore, the specification does not describe the claimed compounds in such full and concise terms so as to indicate that the applicant had possession of these compounds at the time of filing of this application. Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 USC 112 is severable from its enablement provision. (See page 1115.).

Claims 1 and 3-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and reducing smooth muscle migration and/or proliferation via the direct delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries, does not

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reasonably provide enablement for a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 1 and 3-20 are drawn to a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit.

The instant invention specification provides methodologies for inhibiting restenosis by suppressing intimal thickening and hyperplasia in a rat carotid injury model by improving reendothelialization, vascular endothelial function, and reducing smooth muscle migration and/or proliferation via the bolus, sustained, direct and local perivascular delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries (see Example 2).

The instant specification contemplates the prophylactic use of an oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit in restenosis. However, the specification as filed only teaches the inhibition of restenosis via the direct delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries.

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The specification does not provide particular guidance or particular direction for a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, using any oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit. Further, the specification does not provide particular guidance or particular direction for a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, using any oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, other than SEQ ID NOs. 1 and 2 (see 35 U.S.C. 112, first paragraph rejection against claims 1 and 3-20 for written description above).

The description does not provide particular guidance or particular direction for a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, using any oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, and therefore, one of ordinary skill in the art at the time of the invention would have required an undue amount of experimentation to make and use the claimed invention

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commensurate with the full scope of the claims. Due to the lack of specific guidance in the specification as filed and the lack of correlation between inhibiting restenosis by suppressing intimal thickening and hyperplasia in a rat carotid injury model by improving reendothelialization and reducing smooth muscle migration and/or proliferation via the bolus, sustained, direct and local perivascular delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries, and a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, one of skill in the art would have to engage in trial and error experimentation to practice the claimed invention over the scope claimed. The quantity of experimentation required to practice the invention over the scope claimed would include the de novo determination of how to engineer and deliver at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, such that a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury would be developed, where only a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and reducing smooth muscle migration and/or proliferation via the direct delivery of SEQ ID NOs. 1 and 2 to injured carotid arteries is taught.

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 1 and 3-20 are rejected under 35 U.S.C. 103(a) as being obvious over Rosenberg et al. [U.S. Patent No. 5,593,974] ('974), in view of Rosenberg [WO 93/08845] ('845), as evidenced by Noiseux et al. (Circulation 2000 Vol. 102:1330-1336).

Claim 1 is drawn to a method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit. Claims 3-20 depend from claim 1 and include all the limitations of claim 1, wherein the oligonucleotide is in a physiologically compatible solution and applied using an infusion pump, stent, or catheter, (claims 3 and 4), wherein the oligonucleotide further comprises an antisense complementary to c-myb, NMMHC and PCNA (claim 5), wherein the oligonucleotide comprises about 14 to 38 nucleotide bases (claim 6), is treated to render it resistant to degradation by intracellular enzymes (claims 7, 8, and 9), is delivered in a concentration of between approximately 30 and 3000 μg per square centimeter (claim 10), is incorporated into a carrier which is liquid at a temperature below 37°C and comprises polyoxethylene oxide and polypropylene oxide copolymer (claims 12-18), is deposited extravascularly (claim 19) or beneath an adventitial surface of the blood vessels (claim 20).

Rosenberg et al. ('974) teach a method for inhibiting restenosis comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding c-myb, NMMHC and PCNA (see '974, claims 1 and 18, for example), wherein the oligonucleotide is in a physiologically compatible solution and applied using an infusion pump, stent, or catheter, (see '974, claims 2 and 3, for example), wherein the oligonucleotide comprises about 14 to 38 nucleotide bases (see '974, claim 1, for example), is treated to render it resistant to degradation by intracellular enzymes (see '974, claims 4-6, for example), is delivered in a concentration of between approximately 30 and 3000 μg per square centimeter (see '974, claim 7, for example), is incorporated into a carrier which is liquid at a temperature below 37°C and comprises polyoxethylene oxide and polypropylene4 oxide copolymer (see '974, claims 9-20, for example), is deposited extravascularly (see '974, claim 16, for example) or beneath an adventitial surface of the blood vessels (see '974, claim 17, for example).

Rosenberg et al. ('974) do not teach method for preventing restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit.

Rosenberg et al. ('845) teach a method for inhibiting restenosis *in vivo* comprising directly depositing onto a surface an oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit (see Figure 7 and page 20, for example).

Noiseux et al. teach PDGFR- β subunit antisense treatment improves reendothelialization, vascular endothelial function, and reduces smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury (see Abstract, for example).

It would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to devise a method for inhibiting restenosis by improving reendothelialization, vascular endothelial function, and by reducing smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury, comprising directly depositing onto a surface or within the blood vessel, at least one oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit. One of ordinary skill in the art would have been motivated to substitute the oligonucleotide complementary to a nucleic acid encoding c-myb, NMMHC and PCNA taught by Rosenberg et al. ('974) with the oligonucleotide complementary to a nucleic acid encoding PDGFR- β subunit taught by Rosenberg et al. ('845) to devise a method of inhibiting restenosis. One of ordinary skill in the art would have expected success in substituting the oligonucleotide complementary to a nucleic acid encoding c-myb, NMMHC and with the oligonucleotide complementary to a nucleic acid encoding PDGFR- β subunit since Rosenberg et al. ('845) taught oligonucleotides complementary to a nucleic acid encoding PDGFR- β subunit could inhibit translation or transcription of a target nucleic acid sequence *in vivo* and inhibit restenosis.

It is noted that the method for inhibiting restenosis comprising directly depositing onto a surface an oligonucleotides complementary to a nucleic acid encoding a PDGFR- β subunit of Rosenberg et al. ('845) would inherently improve reendothelialization, vascular endothelial function, and reduce smooth muscle migration and/or proliferation within a blood vessel of a

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mammal suffering a vascular injury, as evidenced by Noiseux et al. Since the claimed methods involve only one step, namely directly depositing onto a surface or within the blood vessel an oligonucleotide complementary to a nucleic acid encoding a PDGFR- β subunit, and this step is recited in the methods of Rosenberg et al. ('845), there is no evidence of record to show that the methods of Rosenberg et al. ('845) would not inherently improve reendothelialization, vascular endothelial function, and reduce smooth muscle migration and/or proliferation within a blood vessel of a mammal suffering a vascular injury.


Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (703) 306-3221. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

tcg
August 20, 2003


KAREN A. LACOURCIERE, PH.D
PRIMARY EXAMINER